REMARKS

1. General Matters

1.1. The Examiner refused to consider references CB and CE, stating:

> Reference "CB" was stricken from the IDS. The record should make it clear that a translation was provided only for claims 1-7.
>
> Reference "CE" was stricken from the IDS. The should make it clear that a translation was provided only for the abstract. The following format could be used:
> **Abstract of** Tanikawa (*Adv Med Sci* 155 623, 1990).

It is respectfully submitted that the refusal to consider references was improper. Applicant are permitted, indeed encouraged to submit foreign language documents. In the case of a foreign patent, they are required to submit a copy of the entire document. 37 CFR 1.98(a)(2)(i). In the case of a nonpatent publication, they have discretion to provide a copy of either the entire publication, or that portion which caused it to be listed. 37 CFR 1.98(a)(2)(ii).

For a foreign language reference, the applicants are also required to provide (1) a concise explanation of the relevance of a reference, see 37 CFR 1.98(a)(3)(i), and, if readily available, etc., (2) a copy of a whole or partial English translation, see 1.98(a)(3(ii). If provided, the translation may and usually does also serve to explain the relevance of the reference.

Nothing in 37 CFR 1.98 requires that if a partial translation is provided, that the list required by 1.98(a)(1) specify which portions of the foreign language reference were translated.

It is also clear from the rejection that the Examiner had no trouble reading the English translations and ascertaining what portions of the references they translated.

We have submitted a revised list which includes the additional information suggested by the Examiner, but we wish to make it clear that the references could and should have been considered without it.

2. The Examiner has held that claims 39-40 are directed to a different invention (gastrectomy plus vagotomy) than the invention of claim 1 which was originally elected (only gastrectomy required). The Examiner suggested that claims 39-40 have a combination/subcombination relationship to claim 1, but has not addressed the logical implication of this suggestion.

Restriction in this case is governed by international unity rules. The PCT Administrative Instructions, Annex B, part 1, paragraph (c) "Independent and Dependent Claims" says that "no problem arises in the case of a combination/subcombination situation where the subcombination claim avoids the prior art and the combination claim includes all the features of the subcombination". (The domestic rule is similar, see MPEP 806.05(c).) Hence claims 39 and 40 should be rejoined if claim 1 is deemed allowable.

The Examiner should further consider whether the features of claims 39 and 40 should be considered "corresponding technical features" given the statement of record that vagotomy can occur inadvertently as a result of a gastrectomy, see last response, middle of page 9.

We also note that the Examiner goes further and on page 3 asserts that "it is impossible to perform a gastrectomy without also performing a vagotomy". Were this true -- it is not what applicants asserted-- then claims 39 and 40 would merely be making explicit, an implicit requirement of claim 1, and the holding of constructive election would be improper.

The enclosed Jansson declaration, section 10, states that "about 99% of all gastrectomies are accompanied by a subdiaphragmal vasectomy". That being the case, we consider it appropriate that the holding of constructive election be withdrawn.

1.2. Claims 1 and 38, and new claim 41 now recite that the agent may be a "salt" of ghrelin or a ghrelin analog, consistent with claim 2.

2. Obviousness Issues

2.1. Claims 1, 14, 15, 22, 27, 28, 30 and 38 stand rejected as obvious.

The Examiner argues

(1) the primary references (Zittel, Saidi and Liedman) and disclose that gastrectomy causes weight loss,

(2) the secondary references (Wren, Asakawa) all disclose that ghrelin stimulates appetite, and

(3) hence it would have been obvious to administer ghrelin to reverse the adverse effects of weight loss cause by the gastrectomy.

2.1.1. We previously argued that Asakawa taught away from such use, at least in the situation wherein the gastrectomy was accompanied by intentional or unintentional vagotomy.

The Examiner says that Applicants "have declined to identify the passage" wherein Applicants teach that "if a surgeon were to deliberately perform a vagotomy, ghrelin will be rendered ineffective".

At pages 8-9 of the last response, we quoted page 4, lines 13-16 of the specification as stating

> Even though ghrelin has been found to be an appetite stimulatory signal, it has been noted that this stimulatory effect is lost after vagotomy (Asakawa, supra) giving rise to the notion that for a proper action of ghrelin the presence of the stomach is required.

Asakawa's abstract states: "Ghrelin exhibited gastroprokinetic activity... and potent orexigenic activity..., which was lost after vagotomy".

Later on page 342, col. 1, Asakawa declared

> Moreover, we investigated whether the feeding stimulatory effect of ghrelin is

> associated with a vagally mediated pathway using mice that had undergone truncal vagotomy. Although vagotomy is an invasive procedure, vagotomy eliminated the stimulatory effects on feeding induced by IP injection of ghrelin (Figure 3D). A significant increase of hypothalamic NPY mRNA expression induced by IP administered ghrelin was also abolished by vagotomy (not shown).

See also page 341, figure D.

The Examiner is reminded that a vagotomy can occur accidentally, in the course of a gastrectomy. In this regard, the Examiner's attention is respectfully directed to paragraph 10 of the Jansson Declaration

> In the cause of performing a gastrectomy a vagotomy may occur. In almost 100% of all gastrectomies, a subdiaphragmal vagotomy is also done due to the fact that it is technically impossible or very difficult to avoid the latter surgical procedure (Schwartz's Principles of Surgery:A Modern Approach, Edition 8, Ed: FC Bruncardi et al 2004 Chapter 25).

The Examiner argues that even if Asakawa teaches that a vagotomy prevents ghrelin stimulation of feeding, "this ground of rejection does not depend on Asakawa".

We are not precisely sure what the Examiner means by this. The stated rejection cites two secondary references, one of which is Asakawa. Yes, that means that the Examiner could choose to revise the rejection so the sole secondary reference is Wren. But until he does so, he is relying on Asakawa.

Moreover, such revision would not render Asakawa irrelevant. The obviousness of an invention is determined against the backdrop of the prior art as a whole, including prior art not relied on by the Examiner. If Asakawa "teaches away" from the present invention, it must be considered.

It is of course desirable to determine whether the teachings of Wren and Asakawa are contradictory. They agree that in a

normal individual (i.e., one with an unimpaired digestive system), ghrelin stimulates appetite.

Wren studied the effect of ghrelin in "fasting subjects" who had a "normal physical examination". It may fairly be inferred that these subjects had not experienced either a gastrectomy or a vagotomy, as such would certainly have been mentioned in the description of the research design.

Hence, Wren's teachings do not contradict and therefore do not even potentially diminish the "teaching away" effect of Asakawa.

Nor do the primary references undermine the "teaching away". Indeed, it should be remembered that the weight loss following gastrectomy was experienced despite (one may safely infer) some level of endogenous production of ghrelin.

Formally speaking, a "teaching away" like that of Asakawa goes to the issue of "motivation" and thus to whether or not there is even a prima facie case of obviousness[1].

2.1.2. Even if a prima facie case existed, applicants could seek to rebut it by arguing the existence of "unexpectedly superior results".

The Examiner seeks to forestall such an argument. Referring to the compound disclosed on pp. 47-48 of the spec., he comments (paragraph bridging pp. 7-8):

> Applicants have asserted that as a result of (administration of) this compound, they could detect a slight increase in the amount of fat present in one of the rats. Perhaps the increase in weight of the fat was 1%, perhaps it was 0.01%. One can only speculate. Perhaps the increase in fat weight was statistically significant, and perhaps not. Moreover, the compound that was administered is a growth hormone secretagogue (Patchett, *Proc Natl Acad Sci* 92, 7001, 1995). Perhaps one can argue that

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[1] Asakawa would still have a "teaching away" effect even if there were errors in Asakawa's protocol (cp. section 3.1) because at the time of filing applicant's results were not publicly available to challenge Asakawa's implications.

> this is an "analog" of ghrelin, but at best, it exists only at the periphery of the invention. Certainly, applicants have presented nothing that would qualify as an "unexpected result" insofar as the peptides of claim 7 or 9 is concerned.

Enclosed herewith is an expert declaration from Jansson which quantifies the "fat pad" assay and shows that the increase is statistically significant (paragraph 7). It also explains why MK677 is considered a representative ghrelin analogue (Paragraph 9). And it opines that the data show that MK677 treatment normalizes weight gain in individuals (paragraph 6), that the experiment follows industry norms for ascertaining drug effectiveness (paragraph 8), and that it was properly concluded that ghrelin analogues (like MK677) enhance body weight in gastrectomized rats.

2.2. Claims 1-9 and 38 are rejected as obvious over the above art, further in view of Hosoda. This rejection thus has the same problems as the first rejection.

2.3. Claim 38 is rejected as obvious over Wren or Asakawa.

In the paragraph bridging pp. 9-10, the Examiner states:

> Claim 38 encompasses a method of inhibiting loss of appetite in a subject who has not actually undergone gastrectomy. Claim 38 requires only that the person have the intent to have the surgery done at some point in the future. The "future" could be 2 weeks, or the future could be 20 years hence. As such, the phrase "prior to gastrectomization" exerts little impact. As it happens, a persons' intent with regard to elective surgery has no bearing on his (or her) physiological response to a peptide.

Claim 38 recites "prior to, during, or after gastrectomization". We have split claim 38 into an amended 38 which is strictly therapeutic in nature and new 41 which is strictly prophylactic in nature. This clearly is merely a change in presentation and does not raise new matter issues.

Thus, we have amended claim 38 to recite administration during or after gastrectomization. New claim 41 requires administration prior to gastrectomization, but recites an explicit gastrectomization step so it doesn't depend on "intent". The administration must be at a "prophylactically effective time prior to the gastrectomization, which presumably is shorter than "20 years".

2.4. Claim 38 is also rejected as obvious over Wren or Asakawa, further in view of Hosoda. This rejection would be traversed based on the "teaching away" by Asakawa.

3. Enablement

3.1. The Examiner claims that "as applicants have asserted, Asakawa... supports the position that it is impossible to perform a gastrectomy without also performing a vagotomy, and once a vagotomy is performed, ghrelin loses all activity".

Actually what we asserted was

1. "A vagotomy is 'often performed in combination with gastroenterostomy or partial gastrectomy'", and
2. "Additionally, the vague nerve may be unintentionally damaged during the course of gastrectomy".

In the last response, at no point did we assert, or argue that Asakawa asserted, that it was "impossible" to perform a gastrectomy without also performing a vagotomy. (The new Jansson declaration, para. 10, states that at least subdiaphragmal vagotomies are performed in almost 100% of gastrectomies because it is usually "very difficult" to avoid.)

Moreover, we find it peculiar that the Examiner assumes, for purposes of enablement, that Asakawa teaches that a vagotomy blocks ghrelin stimulation of appetite, while denying this in the prior art rejection. The PTO needs to take a consistent position.

With respect to claims which require vagotomy, it might have been reasonable for the PTO to argue prima facie non-enablement,

based on Asakawa, if the present application were speculative in nature. However, in our Example 1, the "gastrectomy was accompanied by total vagotomy at the level of cardia", but animals treated with the ghrelin analogue MK-0677 (page 47, line 29 and page 48, lines 4-5) nonetheless stimulated appetite and gain in body weight.

So we have evidence of enablement which rebuts the prima facie case based on Asakawa (and any implications of paragraph 10 of the Jansson declaration).

The reason for the discrepancy between our results and that of Asakawa is not known.

A possibility is that the vagotomized animals in Asakawa's study were not in optimal physical condition at the time of the tests. For instance, these animals could have been unable to increase food intake due to suboptimal surgical procedure rather then due to the vagotomy itself. This has been suggested in Arnold et al, al J. Neurosci 26:11052, 2006, copy enclosed, wherein data supporting of the data of the application is presented. (It is further noted that this Arnold article describes Ghrelin, and the discrepancies thus can not be attributed to the use of MK677 versus Ghrelin.)

Another possibility is that the removal of the stomach during a gastrectomy may explain why we see a larger effect, as it may reduce the basal level of ghrelin more than does a vagotomy as performed by Asakawa. Asakawa apparently performed a truncal vagotomy without also performing a gastrectomy.

We do not believe that it is extraordinary that different results are obtained by different groups working on the same or similar subjects. In science, it is not unusual to find that data obtained in the early phase of exploration of a new field of science is disputed by later received data. The old data may be discredited, or distinguished.

Regardless of the reasons why Asakawa didn't see ghrelin stimulation in vagetomized individuals and we did, applicants are

entitled to rely on their own data as evidence of enablement and utility.

There are also procedural issues with this rejection. It sounds like it is questioning whether ghrelin could be operable in a vagotomy context, in which case we should have received a dual 101/112 ¶1 rejection, with "utility" standards applied. See MPEP 2164.07.

3.2. The Examiner has also questioned the term "prophylactically effective" in claim 38, which he reads (contrary to common practice) as requiring "outright prevention".

We cited PTO practice, and the Examiner says in response (page 4, last full paragraph):

> Applicants have argued that other examiner have abstained from rejecting this term (prophylaxis), and that if one examiner abstains from imposing a rejection in a particular situation, all other examiners will follow that examiner are obligated to do the same. According to this line of reasoning, all Supreme Court decisions would have to be decided by a 9-0 vote. The reality is that one examiner is not bound by decisions may by other examiners. And even if they were, the next question would be, who should follow whom? Should it be the examiners who have chosen to reject, or the examiners what have chosen to abstain from rejection?

The "reality" is, firstly, that the MPEP requires examiners to give "full faith and credit" to actions of prior examiners on the same case. They aren't bound but they do need to give deference. See MPEP 704.01, under the heading "previous Examiner's search". So the concept of one examiner following another is not "alien" to PTO practice.

Secondly, the "reality" is that the courts have said that when there have been a significant number of patents issued which imply the acceptance that particular language has particular meaning or is definite, or that particular subject matter is useful and can be practiced without undue experimentation, that may be relied on as evidence in favor of that holding.

The following cases illustrate the relevance of prior patents:

> Ex parte Brian, 118 USPQ 242, 245, (POBA 1958) (past practice of office in accepting definiteness of "fingerprint" claims);
> In re Chakrabary, 596 F.2d 952, 985-86 (CCPA 1979) (product claims reciting microorganisms previously treated as directed to statutory subject matter);
> Andrew Corp. v. Gabriel Electronics, Inc., 6 USPQ 2010, 2012 (Fed. Cir. 1988) (term "substantially" is "ubiquitous" in patent claims and therefore considered definite);
> In re Cortright, 49 USPQ2d 1464 (Fed. Cir. 1999) (Construction of "restore hair growth" for purpose of determining both §112 enablement and §101 utility; prior art references may be indicative of how a claim term will be interpreted by those of ordinary skill in the art);
> Vitronics Corp. v. Conceptronic Inc., 39 USPQ2d 1573, 1578-9 (Fed. Cir. 1996) (prior art used to demonstrate how a disputed term is used by those skilled in the art, and indeed is more objective and reliable than post-litigation expert opinion testimony);
> Pioneer Hi-Bred International v. J.E.M. Ag Supply Inc., 49 USPQ2d 1813, 1819 (N.D. Iowa 1998) (issuance of Boehm USP 2,048,056 in 1936 is evidence that "in those instances where inventors showed they could define a reproducible plant meeting the limits of §112, plant patents were issued under §101".)

So, we are not setting one prior examiner's opinion against Examiner Lukton's, but rather the opinions of all of the Examiners who allowed "prophylactically effective" language in a claim, or "percent prevention" in a claim, against his opinion.

The term "prophylactically effective" appears in the claims of 366 patents issued since 1976 (Ex. A).

The term "prophylactically or therapeutically effective" appears in the claims of 66 such patents (Ex. A).

The terms "prevent", "prevents" or "preventing" appear, together with "disease" or "disorder", in the claims of 2512 patents (Ex. A), and there of course will be other patents which instead cite a specific disease.

Given the difficulties (urged by the Examiner) of establishing absolute prevention, it is unlikely that all, or

even most, of these patents presented evidence of absolute prevention.

The Examiner says, in the paragraph bridging pp. 4-5

> Applicants have also argued that one could consult a dictionary or encyclopedia. The Webster's 9th edition recites that one meaning of the term "prophylactic" is preventative; the term "prevent", in turn, can mean "to keep from happening". Notwithstanding the foregoing examiner would agree that the term "prophylactic" encompasses the possibility that absolute prevention is not achieved. But the term does also encompass the possibility that it is. If there is descriptive support for it, applicants could use an alternative terminology which is consistent with the meaning that they are ascribing to "prophylactic".

We have never asserted that the term "prophylactic" doesn't "encompass" absolute prevention. Rather, we said that it is not limited to absolute prevention.

Webster's New Twentieth Century Dictionary (2d ed 1983) defines "prophylactic" as "in medicine, preventive; protecting against disease". But that doesn't require absolute prevention. "Prevent" is defined by meaning (#3) as "to keep from happening, to make impossible by prior action, to hinder". The term "hinder" doesn't sound absolute to me.

In any event, a patent is addressed to people skilled in the art, and the technical meaning of "prophylactically effective" prevails over any general meaning reported in Webster's.

In conclusion, the examiner's interpretation of "prophylactically effective" in claim 38 is not reasonable.

4. Definiteness

The Examiner says (p. 5) concerning claim 38:

> Claim 38 is drawn to a method of treating disorders in a subject who has not actually undergone gastrectomy. At the same time, the claim requires that the disorder that is being treated be attributable to

gastrectomy. Thus, there is a contradiction; which limitation controls?

There is no contradiction. When a drug is given prophylactically, the condition it is intended to respond to has not yet occurred. We know loss of body weight, body fat and appetite are generally attributable to gastromectization. We can administer a ghrelin or a ghrelin analogue to an individual prior to, but in anticipation of, gastromectization.

Amended claim 38 no longer covers administration prior to gastrectomization. New claim 41 does, but explicitly recites subsequent gastrectomization.

Respectfully submitted,

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Enclosures
-revised PTO-1449
-Jansson Declaration (3 pp.)
-Exhibit A re terms in patent claims
-Arnold, et al. (2006)

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